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Handedness, Functional Cerebral Hemispheric Lateralization, and Cognition in Male-to-Female Transsexuals Receiving Cross-Sex Hormone Treatment

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This study examined the impact of sex hormones on functional cerebral hemispheric lateralization and cognition in a group of male-to-female transsexuals receiving cross-sex hormone therapy compared to eugonadal men with a male gender identity. Cerebral lateralization was measured with a handedness questionnaire and a visual-split-field paradigm and cognitive tests sensitive to sex hormone exposure (identical pictures, 3-D mental rotation, building memory) were also administered. Endocrine measures on the day of participation for transsexual and control subjects included total testosterone, free testosterone, estradiol, gonadotropins, and sex hormone binding globulin concentrations. Compared to controls, male-to-female transsexuals had elevated estradiol and sex hormone binding globulin concentrations and suppressed testosterone concentrations. Transsexual subjects showed a trend toward less exclusive right-handedness than controls. No group differences were observed on the visual-split-field or cognitive tasks. No direct associations were observed between endocrine measures and the laterality measures and cognitive performance. Previous observations of female-typical patterns in cerebral lateralization and cognitive performance in male-to-female transsexuals were not found in the current study.

KEY WORDS: transsexualism; gender identity disorder; estrogen; testosterone; memory; perception.

INTRODUCTION

On average, males and females perform differently on certain measures of cognition and functional hemispheric lateralization, and sex hormones influence these differences (Collaer & Hines, 1995; Maccoby & Jacklin, 1974; McGlone, 1980; Wisniewski, 1998). For example, males are superior at processing visuospatial information (Linn & Peterson, 1985) while females excel at processing verbal information (Maccoby & Jacklin, 1974). Females are more strongly right-handed than males (McGlone, 1980), while males exhibit stronger patterns of hemispheric asymmetries on tests of perception and cognition than females (Wisniewski, 1998). Sex differences in cognition and lateralization can be attributed to both organizational (i.e., permanent effects, usually early in development) and activational (i.e., transitory effects, usually later in development) actions of gonadal steroids in the general population (Cherrier, Craft, & Matsumoto, 2003; Janowsky, 2002; Janowsky, Chavez, & Orwoll, 2000; Sherwin, 2003). Less clear is the role for these hormones in influencing cognition and lateralization in transsexuals receiving cross-sex hormone therapy.

Cognition and Lateralization in Male-to-Female Transsexuals

Male-to-female (MF) transsexuals exhibit feminized/demasculinized patterns of cognitive performance. In one study, verbal memory was superior, a

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female-typical pattern, in MF subjects compared to same sex controls (Cohen-Kettenis, van Goozen, Doorn, & Gooren, 1998), and estrogen treatment enhanced immediate and delayed verbal memory in MF subjects receiving cross-sex hormone therapy (Miles, Green, Sanders, & Hines, 1998). In contrast, visuospatial ability was poor in MF subjects, when compared to same sex controls (van Goozen, Slabbekoorn, Gooren, Sanders, & Cohen-Kettenis, 2002; but see Haraldsen, Opjordsmoen, Egeland, & Finset, 2003), and this demasculinized cognitive pattern was also observed in prepubertal boys with gender identity disorder (Zucker & Bradley, 1995).

Regarding lateralization, pre-pubertal boys with gender identity disorder were more likely to be left-handed than those with a male gender identity (Zucker, Beaulieu, Bradley, Grimshaw, & Wilcox, 2001). When handedness was assessed in adult MF subjects, decreased exclusive right-handedness was observed both prior to (Cohen-Kettenis et al., 1998) and during cross-sex hormone therapy (Green & Young, 2001; Orlebeke, Boomsma, Gooren, Verschoor, & Vanden Bree, 1992; Watson & Coren, 1992). MF subjects who received cross-sex hormone therapy and control women exhibited less functional asymmetry on non-speech, dichotic listening tests compared to men (Cohen & Forget, 1995). No difference in lateralization was observed prior to cross-sex hormone therapy between early onset MF subjects and heterosexual control men on a non-speech, dichotic listening task (Cohen-Kettenis et al., 1998).

Cognition and Lateralization in Female-to-Male Transsexuals

Female-to-male (FM) transsexuals exhibit masculinized/defeminized patterns of cognitive performance. For example, visuospatial abilities were superior (van Goozen et al., 2002) and verbal memory was inferior (Cohen-Kettenis et al., 1998) in FM subjects compared to same sex controls prior to cross-sex hormone therapy (but see Haraldsen et al., 2003). Visuospatial abilities improved and verbal abilities decreased in FM subjects following three months of androgen treatment (van Goozen, Cohen-Kettenis, Gooren, Frijda, & Van de Poll, 1994) and the masculinizing effects of androgen treatment on visuospatial ability persisted for five weeks after cross-sex hormone therapy was stopped (Slabbekorn, van Goozen, Megens, Gooren, & Cohen-Kettenis, 1999).

Similar to MF subjects, FM subjects were less exclusively right-handed than would be expected for genetic females (Cohen-Kettenis et al., 1998; Green & Young, 2001; Orlebeke et al., 1992). Also similar to MF subjects, a dichotic listening test of digit pairs by FM subjects prior to physician-prescribed hormone therapy showed no difference in lateralization between transsexuals and controls (Cohen-Kettenis et al., 1998).

The present study was designed to investigate the association of cross-sex hormone exposure on cognition and functional lateralization by directly measuring pituitary and gonadal hormones on the same day that cognition and lateralization were assessed in MF subjects. In addition to these hormone measurements, histories concerning the use of cross-sex hormone treatment were obtained. These included the use of unregulated hormone supplements and synthetic steroids not prescribed by a physician. Specifically, the goals of the present study were: (1) To investigate functional cerebral hemispheric lateralization and cognition in a group of MF subjects receiving a well-defined regimen of cross-sex hormone therapy compared to control men, and (2) to directly measure pituitary and gonadal hormones in subjects on the day of participation to identify possible activational actions of these hormones on cognition and lateralization. We hypothesized (1) that cross-sex hormone treatment would result in feminization and/or demasculinization of lateralization and cognitive performance in MF subjects compared to control men, and (2) that group differences in behavior would relate to group differences in endocrine profiles.

METHOD

Subjects

Subjects included 27 MF individuals and 16 control men. Of the active Johns Hopkins patients, participation rate was 78%. Subjects were compensated for their time and effort with their laboratory results at no cost. On average, MF subjects were younger (M = 47.7 years; range, 36–68) than control men ($M = 54.7$ years; range, 31–64) ($t(40) = 2.9$, $p < .05$). Age for one MF subject was not available. Additionally, education level (12 vs. 12+ yrs) was lower for MF subjects (15% reported 12+) than control men (63% reported 12+) ($\chi^2(1) = 10.4$, $p < .01$). The entire sample of subjects was Caucasian, with the exception of one MF subject who was an African American.

The Joint Committee of Clinical Investigations of the Johns Hopkins University School of Medicine, The Johns Hopkins Hospital (Baltimore, MD) approved the research reported here. Written informed consent was obtained from all subjects prior to their participation. Exclusion for study enrollment included evidence of an abnormal male phenotype or genotype (i.e., hypospadias,

cryptorchidism, micropenis or chromosome complement other than 46 XY) or completion of less than 12 years of formal education. The education requirement was chosen to minimize individual variability on the cognitive tests resulting from differences in educational background. MF subjects were recruited during a 1 year period from the Johns Hopkins Hospital if they were active patients in the Endocrine Clinic or from local support groups. MF subjects were self-described transsexuals who received physician-prescribed, cross-sex hormone therapy for at least 3 months prior to participation. Control men who presented consecutively for evaluation of suspected hypogonadism, but were found to be eugonadal, were recruited from the Johns Hopkins Hospital Endocrine Clinic during the same period of time as the MF subjects.

Test procedures were identical for both groups of subjects. A research assistant who was naïve to the hypotheses being tested administered the lateralization and cognitive tests. A research phlebotomist who was naïve to the hypotheses being tested collected serum for endocrine assessment.

Sex Steroid Hormones

To control for diurnal hormone fluctuations, all subjects completed the entire test protocol between 08.00 and 11.30 h. Blood was drawn with serum separator tubes and sera and plasma were separated. Samples were stored at 4°C until analyzed. Samples were analyzed by Quest Diagnostics (Owings Mills, MD) for total testosterone (TT), free testosterone (FT), estradiol (E_2), follicular stimulating hormone (FSH), lutenizing hormone (LH), and sex hormone binding globulin (SHBG) concentrations.

Functional Lateralization

Handedness was assessed using the Edinburgh Handedness Questionnaire (Oldfield, 1971), resulting in a scaled score with exclusive left-handedness rated at one extreme (-1) and exclusive right-handedness at the other ($+1$). Functional cerebral lateralization was measured with a visual-split-field, letter trigram identification task (adapted from Eng & Hellige, 1994). This task consisted of 74 randomly presented computer trials in which nonsense strings of 3 letters were presented vertically to the left visual field/right hemisphere (lvf/RH) for 50% of the trials or to the right visual field/left hemisphere (rvf/LH) for 50% of the trials. The edge of the stimuli nearest to central fixation was situated 1.5° from the center. Each trial began with the presentation of a central fixation cross for 2 sec. This fixation was then followed by a central digit and simultaneously presented letter trigram for 150 ms. A pattern mask proceeded the stimuli for 200 ms. Subjects were instructed to fixate on the central digit and report the identity of that digit, followed by the identity of the letters for each trial, to the experimenter.

Cognitive Test Battery

Each participant was administered a battery of three cognitive tests, in a fixed order, by an experienced technician. These included a female-biased perceptual speed test with a small between sex effect size less than 0.5 (Kimura, 1999), a map memory test that our group found to be sensitive (effect size of 0.7) to estrogen and methylated testosterone treatment in women (Wisniewski, Nguyen, & Dobs, 2002), and a male-biased mental rotations test with a large between sex effect size of approximately 0.7 to 1.0 (Kimura, 1999). All cognitive tests were taken with permission from the Kit of Factor Referenced Cognitive Tests (Educational Testing Services, Princeton NJ). The *Identical Pictures Test* (Ekstrom, French, Harman, & Derman, 1976) measured the ability to match identical items from a series of similar distracter drawings, and is documented to elicit a sex difference in performance that favors females. Subjects were allotted 1.5 minutes to complete 48 test items. The dependent measure was the correct match of a test item to an identical target among a row of similar appearing distracters. The *Building Memory Test* (from Ekstrom et al., 1976) measured the ability to remember specific object locations on a street map. Subjects were allotted 4 minutes to study and memorize a map, and were then provided an additional 4 minutes to respond to 12 test items. The dependent measure for this task was the accurate identification of locations of memorized objects on a test map. The *Cube Comparisons Test* (from Ekstrom et al., 1976) measured the ability to mentally rotate a drawing of a 3-dimensional cube. Subjects were allotted 3 minutes to complete 21 test items. The dependent measure was the correct identification of the mental rotation of each test item.

RESULTS

Sex Steroid Hormone Concentrations

Table I presents mean the hormone concentrations for each group. Control men had normal endocrine profiles at participation. As expected, TT ($t(39) = 8.61$, $p < .001$)

Table I. Mean (SEM) Hormone Concentrations for Participants on the Day of Laterality and Cognitive Testing

	TT ng/dL		FT ng/dL		E_2 pg/mL		FSH mIU/mL		LH mIU/mL		SHBG nmol/L	
Group	M	SEM	M	SEM	M	SEM	M	SEM	M	SEM	M	SEM
Male-to-Female Transsexuals	110.2	31.6	26.9	10.1	310.6	79.2	9.76	3.3	6.9	2.1	71.2	10.5
Controls	559.6	41.4	77.9	6.3	20.5	1.7	5.52	0.6	4.7	0.5	38.26	1.8

Note. TT = total testosterone; FT = free testosterone; E_2 = estradiol; FSH = follicle stimulating hormone; LH = lutenizing hormone; SHBG = sex hormone binding globlin.

and FT concentrations ($t(38) = 3.65$, $p < .001$) were significantly lower in the MF group compared to the control men. TT for one MF subject and for one control subject was not available. FT for two MF subjects and for one control was not available. Additionally, concentrations of E_2 ($t(40) = 2.72$, $p < .01$; unavailable for one control) and SHBG ($t(39) = 2.35$, $p < .05$; unavailable for one MF subject and for one control) were significantly elevated in the MF group. No significant group differences were observed for LH or FSH concentrations (both ps $> .05$; unavailable data for one MF and one control). Specific details regarding physician-prescribed and other cross-sex hormone regimens reported by the MF subjects in the present study have been reported elsewhere (Moore, Wisniewski, & Dobs, 2003).

Functional Cerebral Hemispheric Lateralization

A marginal group difference was observed for handedness between MF (M = 0.49; range, −1.0 to 1.0) and control subjects (M = 0.75; range, −0.3 to 1.0), where MF individuals exhibited a trend toward less exclusive right-handedness compared to control men ($t(40) = 1.75$, $p = .07$; unavailable data for one MF subject).

A marginal group difference was observed for the total number of errors committed, with MF subjects committing fewer total errors than controls (M = 6.2 vs.7.6, respectively; $t(39) = 1.76$, $p = .08$; unavailable data from one MF and one control). When considering total errors according to both group and hemisphere, no significant interaction was found ($F(1,39) < 1$). Fewer total errors were committed when stimuli were presented to the rvf/LH compared to the lvf/RH ($t(39) = 16.6$, $p < .0001$; Fig. 1) for both MF and control subjects.

More last letter errors were committed, compared to first letter errors, as is typical when measuring lateralization with a split-field letter trigram paradigm ($t(39) = 52$, $p < .0001$). For both MF and control subjects, last letter errors were more commonly committed following lvf/RH presentation of stimuli ($F(1,39) = 43.81$, $p < .0001$); Fig. 2). Regression analyses regarding linear relationships between endocrine measures as predictor variables and laterality did not reveal any significant associations between hormone concentrations and handedness or split-visual-field processing (ps $> .05$).

Cognitive Task Performance

Table II presents a summary of cognitive test results for MF and control subjects. No significant group differences were observed on any of the tests employed.

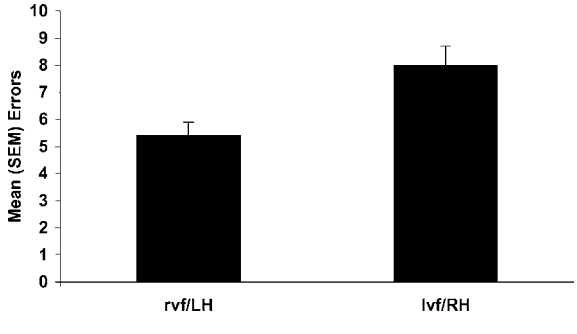

Fig. 1. Mean (+SEM) number of total errors committed by male-to-female (MF) transsexuals receiving cross-sex hormone therapy and eugonadal control men with a male gender identity on the split-visual-field, letter trigram task.

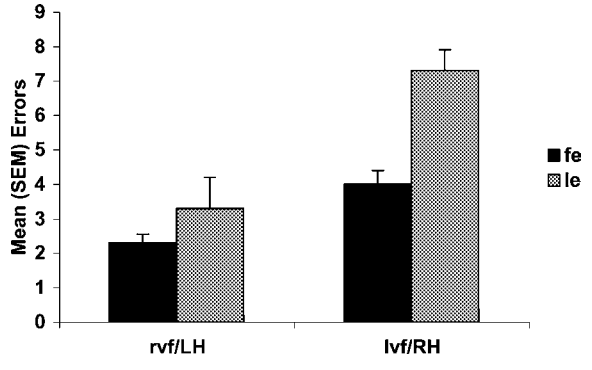

Fig. 2. Mean (+SEM) number of first letter errors (fe) and last letter errors (le) committed by male-to-female (MF) transsexuals and control participants on the split-visual-field, letter trigram task.

Table II. Mean (SEM) Neuropsychological Test Performance

Measure	*M*	SEM		
Identical Pictures				
Male-to-Female Transsexuals ($n = 26$)	28.5	1.3		
Controls ($n = 15$)	26.8	1.6	$t(40) < 1$	ns
Building Memory				
Male-to-Female Transsexuals ($n = 26$)	7.2	0.6		
Controls ($n = 15$)	7.4	0.8	$t(40) < 1$	ns
Cube Rotations				
Male-to-Female Transsexuals ($n = 26$)	6.8	0.8		
Controls ($n = 15$)	5.1	0.9	$t(40) < 1$	ns

Note. Absolute range for identical pictures = 0–48; Building Memory = 0–12; Cube rotations = 0–21.

Once again, linear regression analyses between endocrine measures as predictor variables and neuropsychological performance failed to reveal any significant relationships between hormone concentrations and performance on the three cognitive tasks (all ps $> .05$).

DISCUSSION

Previous studies of hemispheric lateralization and cognition in transsexuals have assessed sex hormone exposure indirectly, via self-report, of physician-prescribed regimens. Unsupervised cross-sex hormone treatment is not uncommon in this group (Feldman & Bockting, 2003), and this appears to be particularly true for MF subjects (Moore et al., 2003). In an attempt to better understand the impact of "real world" cross-sex hormone exposure (i.e., physician-prescribed therapy, herbal preparations, and/or other sources of sex steroids) on laterality and cognition in MF individuals, we obtained hormone regimen histories (Moore et al., 2003) and measured sex steroid hormones and gonadotropins on the morning of laterality and cognitive testing.

Consistent with previous reports, MF subjects in the current study tended to show a pattern of less exclusive right-handedness than control men (Green & Young, 2001; Zucker et al., 2001). In contrast, split-visual-field performance of nonsense trigrams did not differ between groups. While the cause of decreased right-handedness in transsexuals is unclear at this time, it does not appear to be the case that functional lateralization as a whole differs in this group. As we did not observe atypical patterns for processing non-speech stimuli when presented visually to MF subjects, asymmetries for processing non-speech sounds may be unique to the auditory system in MF subjects (Cohen & Forget, 1995).

Our cognitive test battery included three tasks that have previously been shown to be sensitive to sex steroids (Kimura, 1999), two of which had not been previously employed in other studies of transsesxuals (identical pictures and building memory), and a 3-D mental rotation task. MF subjects did not perform better than control men (i.e., the feminized pattern originally hypothesized) on the identical pictures task nor did they perform worse than controls (i.e., the demasculinized pattern) on the 3-D mental rotations and building memory tasks, despite their having significantly elevated estrogen concentrations and suppressed testosterone concentrations. Therefore, sensitivity to small and moderate sex differences and within-sex hormone therapy in the general population are not sufficient characteristics for a cognitive task to elicit group differences in MF individuals receiving cross-sex hormones.

The current study suffered from methodological problems that may have limited our ability to detect group differences in lateralization and cognition between MF subjects and eugonadal men. For example, characteristics related to MF typology such as age at transition, marital status, parenthood, and sexual orientation may differentially predict male-typical versus female-typical behavior (Lawrence, 2003). The current study did not characterize subjects according to these variables, and future studies of lateralization and cognition should do so.

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